FLUID-IMPOSED SHEAR STRESS EFFECTS ON THE GROWTH PROGRAM OF CULTURED VASCULAR ENDOTHELIAL CELLS

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Using cell culture our laboratory has investigated the influence of flow on cell proliferation in bovine aortic endothelial cell (BAEC) monolayers. For subconfluent BAEC monolayers, cell density measurements demonstrate that the rate of proliferation is decreased in the presence of a laminar, steady-state flow. The higher the level of shear stress, the slower the rate of growth, and with a 1 Hz sinusodal, non-reversing pulsatile flow, the inhibitory effect of shear stress is accentuated. ^{3}H-thymidine incorporation and autoradiography data obtained post-shear confirm this influence of flow, indicating that BAEC proliferation is slowed due to a decreased rate of DNA synthesis and is not associated with a loss of cells. Furthermore, flow cytometry demonstrates that this is due to an inhibition of entry into S-phase. Similar results have been obtained for confluent BAEC monolayers. In addition, the process of cell division has been studied using time lapse videos of dividing BAEC. These show that, whereas in static culture BAEC round up to undergo cell division, elongated BAEC in the presence of flow remain flattened in shape while dividing into two elongated daughter cells. These videos also provide evidence of a possible influence of flow on the duration of the various mitotic phases and of cytokinesis, thus further illustrating the effect of flow on the cell division process itself. This influence extends to the gene expression level. This has been demonstrated through alterations in the expression of the proto-oncogene c-myc in response to the agonist, α-thrombin, and in the shear stress-induced enhancement in the expression of c-sis, i.e. platelet-derived growth factor (B chain). These results suggest that both the intrinsic and extrinsic growth program of endothelial cells are influenced by the local flow environment. Of interest are the signal recognition and transduction mechanisms which may regulate these events, and studies in this area are currently in progress.